PROFESSOR KOCH'S REMEDY FOR TUBERCULOSIS.

A FURTHER COMMUNICATION ON A REMEDY FOR TUBERCULOSIS:

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Results of Recent Therapeutic Experience.

Since the publication of my experiences with a new remedy for tuberculosis two months ago, many doctors have been put in possession of the remedy, and have thus been enabled to make themselves acquainted with its qualities by their own experiments. As far as I can judge by the publications that have appeared on the subject, and the letters addressed to me, my statements have, on the whole, found full confirmation. That the remedy exercises a specific action on tuberculous tissue, and can in consequence be employed as a very delicate and certain reagent in searching out hidden, and diagnosing doubtful, tuberculous processes, is agreed on all sides. And in regard also to the therapeutic effect of the remedy, most accounts agree that, in spite of the relatively short duration of the treatment, many patients show improvement, varying only in degree. In not a few cases I am informed that cure even has been attained. Only in some exceptional cases has it been affirmed that the remedy may not only be dangerous in too far advanced cases—which is freely admitted—but that it directly hastens the tuberculous process, that it is in fact harmful *per se*. I myself have had the opportunity during a month and a half of collecting further experiences regarding the therapeutic effect and the diagnostic value of the remedy in about 150 cases of various forms of tuberculosis, and I can only say that all I have lately seen is in harmony with my former observations, and that I have nothing to retract of what I have before stated.[1] So long as the only point of importance was to judge of the correctness of my statements it was not essential to know what the remedy contains, and what its origin is. On the contrary, it was clear that subsequent experiments would be all the more unprejudiced the less was known of the remedy itself, but now that such experiments in sufficient number have been made and have proved the importance of the remedy, the remaining task is to study the remedy beyond the application it has hitherto found, and if possible to apply the principles which lie at the foundation of its discovery to other diseases. This task, of course, demands a full knowledge of the remedy.

The Steps by which the Discovery was made.

I therefore think the right moment has come to make the necessary statements which follow, before I discuss the remedy itself. I think it imperative for the better understanding of its action to trace shortly the steps that led me to its discovery. If a healthy guinea-pig be inoculated with a pure cultivation of tubercle bacilli, the inoculation wound generally becomes sealed, and seems to heal up during the next few days. It is only in the course of from ten to fourteen days that a hard nodule is formed, which soon opens, forming an ulcerating spot which persists until the death of the animal; but the case is very different if an already tuberculous animal be inoculated. The most suitable animals for this experiment are those that have already been successfully inoculated four to six weeks previously. In the case of such an animal also the small inoculation wound becomes sealed at first, but no nodule is formed, a peculiar change taking place at the point of inoculation. Already, on the first or second day, the spot becomes hard and dark-coloured; and this is not confined to the point of inoculation, but spreads around to a diameter of 0.5 to 1 centimètre. During the next few days it becomes more and more clear that the epidermis thus changed is necrotic. Finally it is thrown off, and a flat ulcerated surface remains, which generally heals quickly and completely, without carrying infection to the neighbouring lymphatic glands. Thus the inoculated tubercle bacilli act quite differently on the skin of a healthy guinea-pig and on that of a tuberculous one. But this remarkable action does not belong exclusively to living tubercle bacilli, but also in the same degree to dead ones, whether killed by low temperatures of long duration, which I at first tried, or by boiling heat, or by certain chemicals.

This peculiar fact having been ascertained, I followed it up in all directions, and it was then further found that pure cultivations of tubercle bacilli thus killed, after they have been ground down and suspended in water, can be injected under the skin of healthy guinea-pigs in large quantities without producing anything but local suppuration.[2] Tuberculous guinea-pigs, on the other hand, can be killed by an injection of very small quantities of such suspended cultures, the time being from six to forty-eight hours, according to the dose; a dose which is just insufficient to kill the animal is sufficient to produce a widespread necrosis of the skin in the region of the point of inoculation. If the suspended matter be still more diluted, so that it is scarcely turbid to the eye, the animals remain alive; and if the injections be continued at intervals of one or two days, a noticeable improvement in their condition soon sets in; the ulcer at the point of inoculation becomes smaller, and finally cicatrises. This is never the case without such

[1] As regards the duration of cure, I should like to state here that of the cases which I had provisionally marked cured two have been again received into the Moabit Hospital for further observation, and that for three months no bacilli have been present in their sputum; the physical signs, too, have gradually quite disappeared.

[2] Injections of this nature are among the simplest and most certain methods of producing suppuration free from living bacteria.

treatment. The swollen lymphatic glands become smaller, the condition as regards nutrition improves, and the progress of the disease is arrested, if it is not already so far advanced that the animal dies of debility.

Difficulties in the Way of the Therapeutic Application.

These facts formed the foundation of a therapeutic method against tuberculosis. But an obstacle to the practical employment of such suspensions of killed tubercle bacilli was found in the phenomenon that the tubercle bacilli are by no means reabsorbed, nor do they disappear in any way, but for a long time remain unchanged in their position, producing smaller or larger suppurating centres. Thus it was clear that in this method the curative effect on the tuberculous process is obtained by a soluble substance, diffused, so to speak, into the fluids that surround the tubercle bacilli, and transferred without delay to the circulating fluids of the body, whereas that which has the pus-forming quality seems to remain behind in the tubercle bacilli, or at any rate to be only very slowly dissolved. Thus the only important thing to be done was to carry out the process, which takes place within the body—*outside* of it also—and if possible to extract and isolate the curative substance from the tubercle bacilli. This problem required much work and time before at last I succeeded, by the help of a 40 to 50 per cent. solution of glycerine, in extracting the active principle from the tubercle bacilli. My further experiments on animals, and finally on human beings, were made with liquid thus obtained; and in this way also the liquid which I let other physicians have in order to repeat the experiments was obtained. *The remedy with which the new therapeutic treatment of tuberculosis is carried out is, therefore, a glycerine extract of pure cultivations of tubercle bacilli.*

The Composition of the Remedy.

Besides the active principle there pass from the tubercle bacilli into the simple extract all other substances soluble in 50 per cent. glycerine, and therefore there is found in it a certain quantity of mineral salts, pigment, and other unknown extractive substances. Some of these substances can be removed from it without difficulty, for the active principle is insoluble in absolute alcohol, and can be precipitated by it—not pure, it is true, but in combination with other extractive substances likewise insoluble in alcohol. The colouring matter, too, can be separated out, so that it is possible to obtain a colourless dry substance from the extract which contains the active principle in a much more concentrated form than the original glycerine solution. But this purifying of the glycerine extract has no advantages as regards practical application, as the substances thus removed have no action on the human organism, and the process of purifying would, therefore, only cause unnecessary expense. The constitution of the active principle can as yet be only a matter of conjecture. It seems to me to be a derivative of albuminous bodies, and to be in close relation to them, but it does not belong to the group of so-called toxalbumins, as it can withstand high temperatures, and in the dialysator passes quickly and easily through the membrane. The quantity of active principle present in the extract is, in all probability, very small; I estimate it at fractions of 1 per cent. Thus, if my assumption be correct, we have to deal with a substance the action of which on the tuberculous organism far surpasses that of the strongest drugs known.

Probable Mode of Action of the Remedy.

Various hypotheses may, of course, be formed as regards the specific mode of action of the remedy on tuberculous tissue. Without in any way affirming that my view is the best possible explanation, I imagine the process to be as follows:—The tubercle bacilli in their growth produce in the living tissues—just as in the artificial cultivations—certain substances which have various but always deleterious influences on the living elements of their surroundings—the cells. Amongst these substances is one which, in a certain concentration, destroys living protoplasm and causes it to undergo a transformation into the condition called "coagulation-necrosis," by Weigert. The tissue having become necrotic, this condition is so unfavourable to the nutrition of the bacillus, that it is unable to develop further, and finally in some cases it dies off. In this way I explain the remarkable phenomenon that in organs freshly attacked by tuberculous disease—for instance, in a guinea-pig's spleen or liver filled with grey nodules—numerous bacilli are found, whilst bacilli are rare or entirely absent when the enormously enlarged spleen consists almost entirely of whitish substance in a condition of coagulation-necrosis, such as is often found in guinea-pigs which die of tuberculosis. A solitary bacillus, however, cannot produce necrosis at a great distance, for as soon as the necrosis has reached a certain extent the growth of the bacillus, and, in consequence, the production of the necrosis-producing substance, diminishes, and thus a sort of mutual compensation sets in, and to this it is due that the growth of isolated bacilli is so remarkably restricted, as, for example, in lupus, in scrofulous glands, etc. In such cases the necrosis only extends over a part of the cell, which then, in its further growth, assumes the peculiar form of a giant cell; I thus follow in this statement of my views the explanation of the growth of giant cells first given by Weigert. Now, if the necrosis-producing substance were artificially added to that contained in the tissue surrounding the bacillus, then the necrosis would extend further, and thus the conditions of nutrition of the bacillus would be much more unfavourable than is usually the case. Then, not only would the more completely necrosed tissues disintegrate, slough, and—where this is possible—take with them the enclosed bacilli, carrying them outward; but the baccilli would also be disturbed in their growth to such an extent that they

would die off much sooner than is the case under ordinary conditions. It is in calling forth such changes that, to my mind, the action of the remedy seems to consist. It contains a certain amount of the necrosis-producing substance, of which a correspondingly large dose has a deleterious influence—even in healthy persons—on certain elements of the tissues, probably on the white blood corpuscles or cells closely related to them, thus giving rise to the fever and the whole peculiar complex symptoms. In tuberculous persons a much smaller quantity suffices to cause, at certain spots—that is, wherever tubercle bacilli vegetate and have already impregnated their surroundings with the necrosis-producing substance—a more or less extended necrosis of cells with the accompanying symptoms affecting the entire organism. In this way it is possible to explain—at least for the present—in a provisional way the specific influence which the remedy in certain well recognised doses exercises on tuberculous tissue, as well as the possibility of increasing the doses in so remarkable a fashion, and, finally, to explain the curative effect which the remedy undoubtedly possesses where the circumstances are at all favourable.

REMARKS
ON
THE EFFECT OF KOCH'S REMEDY ON THE INTERNAL ORGANS OF TUBERCULOUS PATIENTS.

Delivered in the Discussion on Professor B. Fraenkel's Paper at the Berlin Medical Society, on January 7th, 1891.

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With reference to a rather large number of preparations which I have brought here, I beg to be allowed to make a few introductory remarks. In the first place, I wish to say that I do not, as will readily be understood, propose to speak here of my own casual observations on patients, but only of what we have been able to establish by way of anatomo-pathological research. From the beginning of the injection period up to the end of the year that has just passed away the total number of deaths of patients treated by injections of Koch's fluid that have come before us has been 21. Besides these we have already had in the course of the present year, I believe, 6 or 7 other cases; even this very day we have had an opportunity of submitting some new specimens to examination.[1]

It is obvious that this anatomo-pathological material must differ considerably from the clinical, in which processes visible to the eye stand in the foreground of observation and of interest, while we are, of course, much more concerned with the internal parts, most of which are inaccessible from the outside, and the diseases of which can in many cases be only very superficially discovered, even by the most accurate examination. Perhaps, however, you will be interested in having the opportunity, even once, of seeing such results, and comparing them with those obtained by the direct examination of parts within reach.

Of the 21 cases which we had up to the end of December, 16 were phthisical in the narrow sense in which the word is usually employed as denoting disease in which the essential element is that the lungs are affected. As regards the other 5 cases, there were among them an exquisite case of severe bone and joint tuberculosis; a case presenting the peculiar complication of carcinoma of the pancreas, with some small smooth-walled cavities with surrounding induration in the apices; a case of empyema in a lying-in woman, who would probably have died even without the injection; a case of pernicious anæmia with very slight old-standing changes in the lungs and tuberculous pleurisy; lastly, a case of tuberculous arachnitis. The other 16 cases were, as I have already said, cases of pulmonary phthisis, in all of which ulcerative processes of greater or less extent were present; most of them were examples of true consumption.

I cannot now enter into the details of these cases; perhaps I may have an opportunity of doing so at some future time. I may, however, be allowed to make some general remarks on them to the following effect: Just as the activity of Koch's remedy, as seen externally, manifests itself principally in the setting up of very acute irritation in the affected parts, with intense redness and great swelling, so does it also in the internal organs. We have seen very marked instances of this. I have here a preparation which may well be taken as a typical specimen. It comes from the clinic of my colleague, Professor Henoch, and belongs to the case of tuberculous arachnitis already referred to. I may observe that there were also changes in the lungs, consisting in some rather old-standing patches of caseous pneumonia, which might be looked upon as the source of metastatic arachnitis, and a number of recent inflammatory changes. After four injections, in all amounting to 2 milligrammes, the last of which was given sixteen hours before death, the patient (a boy, aged 2¾ years) died, and colossal hyperæmia of the pia mater as well as of the brain substance, the like of which I never remember to have seen before, was found. The preparation before you was at first preserved simply in glycerine; it has kept fairly well also in the dry state. It shows on the surface extreme engorgement of the vessels of the pia mater, whilst internally the brain substance is dusky red in appearance. I take this opportunity of mentioning that in this case—the only one, it may be added, of tuberculous arachnitis which has yet come before us for examination—I personally examined the tubercles; I cannot, however, say that I saw any evidence in them of retrogressive changes. The tubercles were very well formed, and presented the usual appearances of meningeal tubercles.

Similar acute hyperæmias and swellings are also seen in other internal parts. In particular it was repeatedly noted by us that even the surface of old pulmonary cavities showed unusually intense redness of the granulation layers; moreover, hæmorrhagic infiltrations of the walls were not seldom present, and even recent hæmorrhages were observed in the cavities. Thus in a man, aged 30, with an old rectal fistula and numerous tuberculous ulcers of the colon, death was the result of hæmoptysis from an old ulcerated cavity; he had received seven injections, the last thirteen days before his death, on which occasion the first bleeding occurred.

The processes observed, however, are not merely transient congestive swellings as to which it may be assumed that they will, perhaps, disappear in a very short time, but there can be no doubt that in the internal parts actual inflammatory processes, and especially active proliferations, occur to an intense degree. This holds good chiefly with regard to two places in which such appearances are very conspicuous; these are, first, the edges of existing ulcers; and next, the neighbouring lymphatic glands, especially the bronchial and mesenteric. The lymphatic glands present a quite unusual degree of enlargement, and notably that form of medullary swelling characteristic of acute irritations, which is caused by rapid proliferation of the cells in the interior of the glands. It is in harmony with these large acute swellings that frequently also an increase in the colourless elements of the blood can be detected—a condition of leucocytosis to which may, perhaps, be attributable the relative frequency with which various infiltrations of white blood corpuscles in the neighbourhood of the affected parts, especially around the tubercles themselves, can be observed.

These swellings occasionally assume a very dangerous character. I will only refer to the phenomena which are seen in the larynx, where, even in cases in which the ulcerated surfaces themselves become clean, the adjoining parts swell to

[1] In addition to this, my assistants have made necropsies in a large number of similar cases in other hospitals and in private, and I have seen the most important results of these examinations.